

# Phosphatidylserine

## Introduction

Phosphatidylserine (PS), a ubiquitous, endogenously occurring phospholipid, is the major acidic phospholipid in the brain. PS and other phospholipids make up the basic structural components of the cell membrane. These membrane phospholipids play an important role in cell-to-cell communication and transfer of biochemical messages into the cell, which trigger cellular responses. The proper functioning of these processes is of ultimate importance, especially in the central nervous system. It is theorized that PS enhances cellular metabolism and communication by influencing the fluidity of cell membranes.<sup>1-4</sup> Oral supplementation of PS has been shown to affect neuronal membranes, cell metabolism, and specific neurotransmitter systems, including acetylcholine, norepinephrine, serotonin, and dopamine.<sup>1-4</sup> Numerous clinical trials have established that PS exerts significant benefit for cognition, especially those functions that tend to decline with age, including memory, learning, vocabulary skills, and concentration.<sup>5</sup>

## Biochemistry

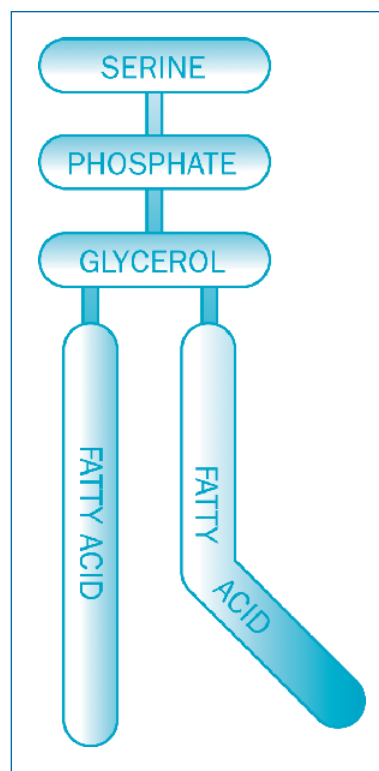
PS is formed in the body from the amino acid L-serine, glycerophosphate, and two fatty acids. Some PS is converted to phosphatidylethanolamine, which is in turn converted to phosphatidylcholine. Phosphatidylethanolamine can also be enzymatically converted to phosphatidylserine; however, these conversions are energy costly.<sup>5</sup>

## Pharmacokinetics

Pharmacokinetic studies indicate exogenous PS crosses the blood-brain barrier, where it appears to have an affinity for the hypothalamus. Oral administration results in peak levels in 1-4 hours.

## Mechanisms of Action

Animal experiments suggest PS has a trophic (growth supportive) effect on the brain. Compared to younger rats, older rats normally have fewer and smaller brain neurons and decreased cell surface-receptor density for nerve growth factor (NGF). These receptors mediate the actions of NGF to enhance neuronal differentiation and other aspects of neuroplasticity. As rats age, they show declines in NGF-receptor density in the cerebellum, hippocampus, and other brain zones. When dosed with PS, older rats retain more and larger brain neurons along with higher NGF-receptor density. In addition, when older rats are subjected to maze tests, a subpopulation that normally tests significantly more impaired than the average shows the most improvement in cognition and NGF-receptor density when dosed with PS.<sup>6</sup>



PS dosing in aged rats increases dopamine release from the striatum and stimulates acetylcholine release from the cerebral cortex, in addition to preventing age-induced loss of dendritic spines in the hippocampal pyramidal neurons and atrophy of cholinergic cells in the basal forebrain.<sup>7</sup>

Human studies using PET scanning to investigate brain glucose utilization in Alzheimer's patients noted increases in glucose utilization in PS-supplemented patients, especially in the temporo-parietal areas, which are specifically affected by Alzheimer's disease (AD).<sup>8-11</sup>

PS may also protect cells from damage produced by free radicals. A significant decrease in damage to cultured human fibroblasts from the enzymatic oxidation of acetaldehyde by xanthine oxidase was noted in cultures pre-treated with PS.<sup>12</sup>

## Clinical Applications

### Age-Associated Memory Impairment/ Cognitive Decline

Studies of phosphatidylserine dosing in age-associated memory impairment indicate PS is an effective remedy for this common malady. The largest of these studies, a multi-center, placebo-controlled study of 494 elderly patients, resulted in significant improvements in behavioral alterations (loss of motivation, initiative, interest in the environment, and socialization), memory, and learning in the PS group (300 mg/day) compared to placebo.<sup>3</sup> At least a dozen other studies, most using 300 mg/day, note similar significant improvements in learning, memory, concentration, and recall.<sup>5</sup>

### Alzheimer's Disease

Phosphatidylserine has received attention for treatment of AD. Generally, PS produces significant improvement in anxiety, motivation, memory, and cognition.<sup>4,8-14</sup> At daily doses of 200-300 mg for up to six months, PS consistently improved clinical global impression and activities of daily living. In a double-blind, placebo-controlled trial involving 425 patients with moderate-to-severe cognitive loss, PS significantly improved memory, learning, motivation, socialization, and general "adaptability to the environment."<sup>3</sup> In another placebo-controlled study of 142 AD patients, PS was given (200 mg/day) for three months, and the patients were followed for 24 months. A subgroup of patients with severe cognitive impairment demonstrated

significant improvements based on the Blessed Dementia Scale (activities of daily living, information processing, personal and non-personal memory) three months after treatment cessation.<sup>15</sup> In other studies, most using 300-400 mg/day, improvement tended to be the greatest in those with less severe cognitive impairment,<sup>4,9-11,13</sup> and in one study were transient, fading after 16 weeks.<sup>8</sup>

### Attention Deficit/Hyperactivity Disorder

Use of PS in combination with omega-3 fatty acids shows promise in the management of attention deficit/hyperactivity disorder (ADHD). Vaisman et al conducted a double-blind trial with omega-3 PS, recruiting 60 children (3:1 ratio of boys:girls) with ADHD-like symptoms (average age 9 years).<sup>16</sup> The children were randomized to three groups: (1) canola oil (controls), (2) fish oil (providing 250 mg DHA/EPA daily), and (3) an omega-3/PS combination (providing 300 mg PS and 250 mg DHA/EPA daily). No stimulant medications or other dietary supplements were administered during the trial period (80-100 days; average 91 days). The group receiving omega-3 PS had the highest proportion of children whose symptoms improved.

The children's sustained visual attention and discrimination were assessed using the Test of Variables of Attention (TOVA). The TOVA ADHD Index normalized score improved over controls for both the omega-3 PS and the fish oil groups, but significantly more in the PS group ( $p < 0.001$ ). This indicates that omega-3 PS improved attention performance (and more dramatically than fish oil) compared to the control group. The omega-3 PS group also manifested a significantly higher ratio of symptom clearance than the control group, with 11/18 of the omega-3 PS children becoming asymptomatic versus 3/21 of the control children ( $p < 0.05$ ). Of the fish oil group, 7/21 became asymptomatic – not statistically significantly different from controls. Omega-3 PS ameliorated the inattention symptoms of ADHD to a greater degree than equivalent amounts of DHA/EPA from other dietary sources.

### Depression

Maggioni et al studied the effects of oral PS (300 mg/day) on depressed geriatric patients not exhibiting dementia and noted significant improvement in depressive symptoms after 30 days. Memory and behavioral symptoms were also improved compared to placebo.<sup>17,18</sup>

## Chronic Stress/Hypercortisolism

It appears PS might modulate cortisol release in stressful situations. In a study of exercise-induced stress, both ACTH and cortisol were lower after exercise in healthy volunteers taking 800 mg/day PS versus placebo. It was thought that PS affected hypothalamic release of corticotropin-releasing factor, an activator of the hypothalamic-pituitary-adrenal axis in response to stress.<sup>19</sup> This may provide some insight into the effect of PS on depression, as hypercortisolism is a common finding in depression.

## Side Effects and Toxicity

The oral LD<sub>50</sub> in rats is >5 g/kg body weight, and no teratogenicity was noted in rats and rabbits; mutagenic testing was negative.<sup>20</sup> In a tolerability and toxicity study of 130 patients, no significant changes were noted in CBC or serum chemistry results, except for a significant decrease in the liver enzyme alanine aminotransferase (ALT) and uric acid levels.<sup>21</sup>

## Dosage

Therapeutic dosages range from 200-800 mg daily, depending on condition. For example, the recommended dosage for AD ranges from 200-400 mg daily, 300 mg daily for ADHD and depression, and 800 mg daily for chronic stress. An optimal daily intake for healthy individuals has not been established. Oral administration of PS is the preferred route of administration.

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